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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/724,727	12/02/2003	Dexiang Chen	036481-0143	2185

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EXAMINER	
CHEN, STACY BROWN	
ART UNIT	**PAPER NUMBER**
1648	

DATE MAILED: 01/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/724,727	CHEN ET AL.	
	Examiner	Art Unit	
	Stacy B. Chen	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 October 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6,7,10-15 and 21-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6,7,10-15 and 21-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/21/05*. and 2/16/05 SBC 1/11/06
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed October 21, 2005 is acknowledged and entered. Claims 1-3, 6, 7, 10-15 and 21-23 are pending and under examination.

2. The objection to the specification for lacking updated priority data information on the first page of the specification is moot in view of Applicant's amendment.

3. The objection to claims 1-23 and 30-35 for reciting a non-elected invention, specifically, a vaccine composition that is an antigen, is withdrawn in view of Applicant's amendment, or moot in view of cancelled claims.

The objection to claims 1-23 and 30-35 for reciting a seemingly redundant term, "into or across the skin", is withdrawn in view of Applicant's explanation. According to the specification, "into the skin" encompasses delivery into the layers of the skin. "Across the skin" refers to delivery through at least a top layer of skin.

4. The rejection of claims 30-35 under 35 U.S.C. 112, first paragraph, for failing to enable the full scope of the claimed invention, is moot in view of the cancellation of claims 30-35.

5. The following art rejections are withdrawn in view of Applicant's amendment to the claims, incorporating an adjuvant composition comprising a CpG motif and an ADP-ribosylating toxin into the particulate composition used to induce an IgA response.

- The rejection of claims 1-7 under 35 U.S.C. 102(b) as being anticipated by Burkoth *et al.* (WO 98/10750, herein, "Burkoth"), is withdrawn in view of Applicant's amendment, or moot in view of cancelled claims.
- The rejection of claims 1, 3-5, 9-14 and 16-19 under 35 U.S.C. 102(b) as being anticipated by Sato *et al.* (*Science*, 1996, 273:352-354, herein, "Sato"), is withdrawn in view of Applicant's amendment, or moot in view of cancelled claims.
- The rejection of claim 15 under 35 U.S.C. 103(a) as being unpatentable over Burkoth in view of Kaiserlian *et al.* (*European J. Dermatology*, 1999, 9(3):169-176, herein, "Kaiserlian", web page printout pages 1-6), is withdrawn in view of Applicant's amendment, or moot in view of cancelled claims.

Claim Rejections - 35 USC § 112

6. (*New rejection*) The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3, 6, 7, 10-15 and 21-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 and all dependent claims recite, "(b) the antigen is derived or obtained from a pathogen". The metes and bounds of the claims cannot be determined because the term, "derived", does not clearly point out what the derived antigen is. The meaning of "obtained" is clear. However, it is unclear what portion of the pathogen or pathogen's antigen is retained in the resulting antigen of (b). It is suggested that terms relating to derivation be removed from the claims to overcome this rejection.

Claim Rejections - 35 USC § 103

7. Claims 1-3, 6, 7, 10-15 and 21-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Burkoth in view of Kaiserlian, and further in view of McCluskie *et al.* (*J. Immunol.* 1998, 161:4463-4466, herein, "McCluskie").

The claims as amended are drawn to a method of generating an IgA antibody response specific for an antigen at a mucosal surface of a vertebrate subject in need thereof. The method comprises:

1) Delivering a particulate vaccine composition into or across the skin of said subject using a transdermal delivery technique, and
2) Coadministering an adjuvant composition to said subject, wherein the vaccine composition comprising a nucleic acid encoding said antigen, and the antigen is obtained from a pathogen that enters said subject's body via a mucosal surface, and the adjuvant composition comprises a CpG oligonucleotide and an ADP-ribosylating toxin.

Specifically, the particulate vaccine composition is delivered using a needleless syringe powder injection device. The antigen is viral or bacterial, and the adjuvant composition is particulate. Also claimed is the delivery of the vaccine into or across the subject's skin using a transdermal delivery technique. The vaccine composition and adjuvant composition are administered to the same site in the subject, and can be administered concurrently, or combined into one composition and administered. The adjuvant is a cholera toxin in combination with a CpG polynucleotide.

Burkoth discloses transdermal (percutaneous) and transmucosal administration of drugs and pharmaceuticals, wherein the drugs and pharmaceuticals are in dry particulate form (page 10, line 32 through page 11, line 19, and page 19, lines 9-11). The administration is via

needleless injection using powdered nucleic acid molecules (Burkoth claims 11-13, and page 1, lines 10-14). Burkoth's method includes nucleic acid immunizations to the stratum basal layer of skin (page 6, lines 3-8). The nucleic acid encodes an immunogenic sequence that serves to elicit a humoral and/or cellular immune response in a subject (page 13, lines 12-16). The nucleic acid sequences encode peptides known to display antiviral and/or antibacterial activity (page 14, lines 16-19). Since the materials and methods of Burkoth and Applicant are similar, namely transdermal delivery of nucleic acid using a needeleless syringe, the outcome of generating a mucosal immune response at a mucosal surface is expected. Further, since a mucosal immune response is expected as a result of Burkoth's method, an antigen specific IgA response would also be expected. An antigen specific immune response would be expected because mucosal immune responses are characterized by the presence of secretory IgA that provides local immunity. In order for the IgA to provide immunity, it must be specific for that particular invading pathogen/antigen. Burkoth does not teach the use of an adjuvant in combination with the vaccine component.

However, Kaiserlian teaches that effective intradermal immunization with DNA requires immunostimulatory sequences, such as CpG (page 3 of webpage printout, second full paragraph). Kaiserlian discloses that DNA vaccines administered in saline are effective without the need for adjuvants or delivery systems, however, intradermal immunizations with DNA have different requirements for an effective immune response. One of ordinary skill in the art would have been motivated to administer an adjuvant with Burkoth's powder vaccine because Kaiserlian teaches that effective intradermal immunization with DNA requires immunostimulatory sequences (Kaiserlian, page 3, second full paragraph). One would have been

motivated to supplement the powder vaccine of Burkoth with CpG nucleotides in order to stimulate a greater immune response. Administering the adjuvant with the vaccine would have been obvious because Kaiserlian teaches that immunostimulatory sequences are often part of the plasmid that contains the vaccine nucleic acid sequence, expressed at the same time. One would have had a reasonable expectation of success that a plasmid containing immunostimulatory sequences, such as Kaiserlian's CpG motifs, along with a vaccine nucleic acid sequence of Burkoth, would have worked as an immunization to generate a mucosal immune response.

The teachings of Burkoth and Kaiserlian are silent on the administration of an additional adjuvant, such as CT (an ADP-ribosylating toxin) in combination with CpG oligonucleotides.

However, McCluskie discloses that the mucosal adjuvant, cholera toxin (CT) is often used with subunit vaccines and demonstrates synergistic effects on both the humoral and cellular immune responses against the vaccine antigen when administered together with CpG motifs (abstract). McCluskie administers hepatitis B surface antigen by nasal inhalation concurrently with CT and CpG (page 4464, column 1, first paragraph).

It would have been obvious to modify the method of Burkoth by co-administering adjuvants. One would have been motivated to include CpG sequences, as taught by Kaiserlian, and to further include CT because McCluskie teaches that CT and CpG act synergistically to generate both mucosal and systemic immune responses. Although McCluskie does not administer the CT and CpG with a nucleic acid component, the nucleic acid of Burkoth/Kaiserlian (encoding an antigen and CpG), would have been expected to be expressed, at which point the mucosal adjuvant effect of the CT and CpG would have taken effect. One would have had a reasonable expectation of success because McCluskie demonstrates that CT

and CpG induced act synergistically to induce a systemic and mucosal immune response against a hepatitis B surface antigen. Therefore, the claims are obvious over Burkoth in view of Kaiserlian and further in view of McCluskie.

Response to Arguments

8. Applicant's arguments rebutting the art rejections have been carefully considered. The only art rejection remaining is the obviousness rejection above, the rejection of claims 1-3, 6, 7, 10-15 and 21-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Burkoth in view of Kaiserlian, and further in view of McCluskie. The arguments specific to this rejection will be addressed. (Applicant's arguments occasionally refer to claim 20 as pending, however, claim 20 was cancelled in the amendment filed October 21, 2005.) Applicant's arguments have been carefully considered, but fail to persuade withdrawal of the rejection. Applicant's substantive arguments are primarily directed to the following:

- Applicant argues that the state of conventional wisdom and immunological dogma just prior to the priority date of the present application was such that no combination of the prior art would have rendered the presently-claimed invention as obvious. In particular, the inventors discovered that the delivery of a particulate vaccine into or across the skin results in the generation of an IgA response at a mucosal surface. As of the date to which the instant application claims priority, the systemic and mucosal immune systems were thought to be quite different to one another, and mucosal administration of a vaccine was thought to generate only mucosal immunity.

- In response to Applicant's argument that one would not have expected the delivery of a particulate vaccine into or across the skin would result in the generation of an IgA response at the mucosal surface, the fact that Applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).
- In this case, if one of ordinary skill had combined the teachings of the prior art as described above, one would have naturally performed the claimed method, though unknowingly. An IgA antibody response at a mucosal would have been induced had one practiced the combined method of Burkoth, Kaiserlian and McCluskie.

- Applicant points to McCluskie for support of the knowledge at the time the instant application was filed. McCluskie discloses that, generally, parenteral antigen delivery induces only systemic immunity whereas mucosal delivery can trigger both mucosal and at local and distal sites, as well as systemic. Applicant concludes that given the state of the art at the time of filing, one would not have been motivated to administer a particulate vaccine into or across the skin of a subject to induce an IgA antibody response at a mucosal surface of a subject. One would have only expected to induce systemic immunity.
    - In response to Applicant's argument, the unappreciated result of inducing an IgA antibody response at a mucosal surface would occur when one practices the combined methods described above. Just because one would not expect an IgA

response at a mucosal surface does not change the fact that an IgA response would have occurred. While Applicant may have discovered a previously unknown benefit of the instant method, the method itself would have been obvious. Applicant has discovered a "side-effect" (IgA response at a mucosal site) of the combined method described above, however, any serendipitous "side-effects" (IgA response at a mucosal site) of an obvious method are inherent.

- Other advantages of the instant invention include ease of delivery, as vaccine administration through the skin is conventional. Also, it is technically less demanding than mucosal delivery and has fewer safety concerns than delivery to the more sensitive mucosal surfaces.
    - In response to Applicant's arguments, the advantages of the instant invention are acknowledged. However, these advantages are not unknown or uncommon. As Applicant stated, vaccination via the skin is conventional, as is needleless injection (see Burkoth).
- Applicant argues that significant modification of Burkoth's method and compositions would have been necessary to arrive at the claimed invention. For example, Burkoth's compositions are in particulate form, while Kaiserlian's CpG motifs are adjuvants in plasmid vaccine compositions. Applicant reasons that because nothing Kaiserlian or Burkoth suggests that Kaiserlian's CpG motifs may be applied to particulate vaccine compositions, one would not have been motivated to use CpG motifs with Burkoth's particulate compositions. Further, McCluskie discloses the use of liquid, not particulate vaccine compositions. Nothing in McCluskie or Burkoth suggests that Burkoth's

formulation could be modified to accommodate McCluskie's liquid approach, or vice versa.

- In response to Applicant's argument that significant modifications need to be made to Burkoth to arrive at the claimed invention, it does not follow that the modifications are not obvious. One would have been motivated to supplement the powder vaccine of Burkoth with CpG nucleotides in order to stimulate a greater immune response. Administering the adjuvant with the vaccine would have been obvious because Kaiserlian teaches that immunostimulatory sequences are often part of the plasmid that contains the vaccine nucleic acid sequence, expressed at the same time. In the same way, use of CT along with CpG as an adjuvant is suggested by McCluskie. It would have been well within the ability of one to administer the adjuvant in an acceptable form, such as particulate, along with Burkoth's particulate vaccine.
- One of ordinary skill in the art would have been motivated to administer an adjuvant with Burkoth's powder vaccine because Kaiserlian teaches that effective intradermal immunization with DNA requires immunostimulatory sequences (Kaiserlian, page 3, second full paragraph).

- Applicant argues that McCluskie teaches that intranasal (mucosal) administration of a DNA vaccine generates an immune response at the nasal mucosal surface. McCluskie does not provide any data relating to delivery of vaccine or adjuvants via the skin or any other non-mucosal route.

- In response to Applicant's arguments against the McCluskie reference individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). McCluskie is not relied upon for teachings regarding administration of DNA vaccine via the non-mucosal routes. Burkoth teaches non-mucosal routes of DNA vaccine administration. McCluskie is relied on for the teachings regarding the combination of CT and CpG. One of ordinary skill reading McCluskie, would be motivated to administer a combination of CT and CpG because they are powerful adjuvants. The combination of references from this standpoint leads one to the instantly claimed invention.

- Applicant also argues that, given the gross differences in the effects of vaccination via the two routes of administration, it would not have been possible to predict from the results of McCluskie that the combination of CpG motifs and ADP ribosylating enzymes would have a synergistic effect on mucosal immunity when delivered to a distant site such as the skin. One would not have been motivated to do this, nor would one have had a reason to expect such a combination to work.

  - In response to this argument, the references as a whole would lead one of ordinary skill to practice the claimed invention. There is motivation to modify Burkoth by adjuvanting Burkoth's particulate vaccine with CpG motif sequences and CT (see rejection). In order to arrive at the claimed invention, one would not have had to

predict a synergistic response between CpG motifs and CT. In the instant case, Applicant has not even disclosed if the two products act synergistically. The inventive concept does not lie in the adjuvant combination, rather the method of delivery of the particulate antigen.

To summarize, the instant invention is obvious over Burkoth's particulate vaccine in combination with the adjuvants taught by Kaiserlian and McCluskie. Applicant argues that the combination would not be *expected* to result in the surprising discovery that the claimed method of administration (particulate vaccine into or across the skin) results in an IgA response at a mucosal site. However, in response, while the expectation of IgA at a mucosal surface via the claimed method may not have been expected, one of ordinary skill practicing the combined method taught by the prior art would have induced an IgA response at a mucosal surface anyway. The fact that Applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious.

Conclusion

9. No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stacy B. Chen whose telephone number is 571-272-0896. The examiner can normally be reached on M-F (7:00-4:30). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James C. Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Stacy B. Chen
January 11, 2006